



## Clinical trial results:

### Tocilizumab for the Treatment of Familial Mediterranean Fever – A randomized, doubleblind, phase II proof of concept study-TOFFIFE

#### Summary

EudraCT number	2016-004505-13
Trial protocol	DE
Global end of trial date	17 June 2021

#### Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

#### Trial information

##### Trial identification

Sponsor protocol code	TOFFIFE
-----------------------	---------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03446209
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University Hospital Tuebingen
Sponsor organisation address	Geissweg 3 , Tuebingen, Germany, 72076
Public contact	Department of Internal Medicine II, University Hospital Tuebingen, +49 7071292980681, joerg.henes@med.uni-tuebingen.de
Scientific contact	Department of Internal Medicine II, University Hospital Tuebingen, +49 7071292980681, joerg.henes@med.uni-tuebingen.de

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2020
Global end of trial reached?	Yes
Global end of trial date	17 June 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of Tocilizumab in patients with active FMF in a randomized, placebo controlled setting

Efficacy: measured by Physician's Global Assessment of disease activity (PGA) at week 16

Primary endpoint will be the number of patients achieving an adequate response to treatment at week 16, defined as: PGA  $\leq$  2 + normalized ESR and/or CRP (the one that led to inclusion must be normalized) + normalized SAA

Protection of trial subjects:

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial act according to Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. This is a scientific clinical study; the German Medicines Act (AMG) §40 is applicable without restrictions according to section §42

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

An enrolment request for a patient will be sent from the site to the CI. After the CI has confirmed, that the subject can be enrolled, a unique subject number for identification purposes will be assigned to the patient in order to maintain his/her anonymity. The subject number will be used for the patient throughout the study.

### Pre-assignment

Screening details:

Screening will be performed within 28 days prior to first administration of TCZ. The investigator will review all information obtained from the screening procedures and will inform the CI via an eligibility form. The CI will confirm, in writing, whether the subject fulfil all criteria for eligibility.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The i.v. medication/placebo will be prepared by an unblinded member of the study group at each center or by the local pharmacy.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tocilizumab arm

Arm description:

Tocilizumab i.v. 8 mg/kg bodyweight (max. 800mg) infusion blinded by cover, every 4 weeks up to week 24.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoAcmtra, Actemra
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab i.v. 8 mg/kg bodyweight (max. 800mg) infusion blinded by cover, every 4 weeks up to week 24

<b>Arm title</b>	Placebo arm
------------------	-------------

Arm description:

NaCl 0.9% infusion blinded by cover, every 4 weeks up to week 24.

Arm type	Placebo
Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NaCl 0.9% infusion blinded by cover, every 4 weeks up to week 24.

<b>Number of subjects in period 1</b>	Tocilizumab arm	Placebo arm
Started	15	15
Completed	13	12
Not completed	2	3
Consent withdrawn by subject	2	3

## Baseline characteristics

### Reporting groups

Reporting group title	Tocilizumab arm
Reporting group description: Tocilizumab i.v. 8 mg/kg bodyweight (max. 800mg) infusion blinded by cover, every 4 weeks up to week 24.	
Reporting group title	Placebo arm
Reporting group description: NaCl 0.9% infusion blinded by cover, every 4 weeks up to week 24.	

Reporting group values	Tocilizumab arm	Placebo arm	Total
Number of subjects	15	15	30
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	15	30
Age continuous			
Units: years			
median	33	28.5	
full range (min-max)	18 to 53	18 to 41	-
Gender categorical			
Units: Subjects			
Female	7	7	14
Male	8	8	16
Disease duration			
Units: years			
median	18	12.5	
full range (min-max)	2 to 44	0 to 29	-
Baseline weight			
Units: kilogram(s)			
median	70	70.5	
full range (min-max)	50 to 140	61 to 117	-
Baseline height			
Units: centimetre			
median	166	170	
full range (min-max)	150 to 180	159 to 183	-
Baseline FFbH			
Hannover Functional Questionnaire Backache (FFbH-R) is a questionnaire for the diagnosis of functional disability caused by backache. German title: Funktionsfragebogen Hannover Rücken (FFbH-R)			
Units: percent			
median	91.7	88.9	
full range (min-max)	66.7 to 100	8.3 to 100	-
DAS28 Disease Score			
Units: points			
median	3.4	3.2	
full range (min-max)	1.2 to 7.2	1.8 to 5.5	-
Baseline VAS patient activity			
The visual analog scale for pain is a straight line with one end meaning no pain and the other end meaning the worst pain imaginable.			
Units: score			

median	58	47	
full range (min-max)	15 to 88	0 to 77	-
Baseline PGA (0-24)			
Units: points			
median	10	8	
full range (min-max)	3 to 17	0 to 17	-
Baseline SAA			
Serum amyloid A (SAA) is the most prominent acute phase reactant as its serum levels in acute phase response demonstrate the most notable increase			
Units: milligram(s)/litre			
median	31	18	
full range (min-max)	1 to 661	3 to 275	-
Baseline CRP			
C-Reactive Protein test measures the level of c-reactive protein (CRP) in your blood. It is seen as a biomarker for inflammation.			
Units: milligram(s)/decilitre			
median	1.4	0.9	
full range (min-max)	0.0 to 15.3	0.2 to 4.2	-
Baseline ESR			
The erythrocyte sedimentation rate (ESR or sed rate) is the rate at which red blood cells in anticoagulated whole blood descend in a standardized tube over a period of one hour.			
Units: millimetre(s)			
median	14	14	
full range (min-max)	4 to 65	0 to 41	-

## End points

### End points reporting groups

Reporting group title	Tocilizumab arm
Reporting group description: Tocilizumab i.v. 8 mg/kg bodyweight (max. 800mg) infusion blinded by cover, every 4 weeks up to week 24.	
Reporting group title	Placebo arm
Reporting group description: NaCl 0.9% infusion blinded by cover, every 4 weeks up to week 24.	

### Primary: Number of patients reaching response to treatment

End point title	Number of patients reaching response to treatment
End point description: The primary endpoint of the trial is to compare Tocilizumab and Placebo in terms of response to treatment. The number of patients reaching response to treatment will be documented for each treatment arm. It will be reached when the PGA < or = to 2, and normalization of SAA and CRP and/or ESR.  2 of the patients (15.4%) of the Tocilizumab arm reached the primary endpoint with a PGA < or equal to 2, normalization of SAA and CRP and/or ESR. None of the placebo arm patients reached the primary endpoint	
End point type	Primary
End point timeframe: 16 weeks	

End point values	Tocilizumab arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Subjects	2	0		

### Statistical analyses

Statistical analysis title	Statistical analysis of the primary endpoint
Comparison groups	Tocilizumab arm v Placebo arm
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.089
Method	Mantel-Haenszel

Notes:

[1] - The proportion of patients who experienced the primary endpoint were compared and statistically assessed using a two sided Mantel-Haenszel chi-square test, stratified by centre, to test the null hypothesis of equal proportions in the two therapy groups.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

16 weeks

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4
--------------------	---

### Reporting groups

Reporting group title	Tocilizumab arm
-----------------------	-----------------

Reporting group description:

Tocilizumab i.v. 8 mg/kg bodyweight (max. 800mg) infusion blinded by cover, every 4 weeks up to week 24.

Reporting group title	Placebo arm
-----------------------	-------------

Reporting group description:

NaCl 0.9% infusion blinded by cover, every 4 weeks up to week 24.

Serious adverse events	Tocilizumab arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Ileitis	Additional description: Inflammation of the Ileum		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Severe disease activity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Tocilizumab arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	8 / 12 (66.67%)	
Cardiac disorders			
Cardiac			
subjects affected / exposed	2 / 13 (15.38%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Infection			
subjects affected / exposed	10 / 13 (76.92%)	5 / 12 (41.67%)	
occurrences (all)	10	5	
FMF flare			
subjects affected / exposed	10 / 13 (76.92%)	4 / 12 (33.33%)	
occurrences (all)	10	4	
Gastrointestinal disorders			
Gastroenterology			
subjects affected / exposed	9 / 13 (69.23%)	2 / 12 (16.67%)	
occurrences (all)	9	2	
Hepatobiliary disorders			
Increased liver enzymes			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	6 / 13 (46.15%)	2 / 12 (16.67%)	
occurrences (all)	6	2	
Musculoskeletal and connective tissue disorders			
Joint complaint			
subjects affected / exposed	6 / 13 (46.15%)	1 / 12 (8.33%)	
occurrences (all)	6	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to insufficient response or side effects, seven (28%) of patients terminated earlier than week 16, which led to missing data at week 16. These early terminations occurred in 4 (33.3%) patients of the placebo arm and in 3 (23.1%) in the TCZ arm.
--

Notes: